Stavrianopoulos et al., Serial No. 08/486,070 (Filed June 7, 1995)
Exhibit 1A

Disclosure of "wells" in the specification to support "generic wells" include the following:

"**plastic or glass wells**, . . . (page 13, last line)

"The portion of the device for containing the fluid is desirably a **well**, . . . " (page 14, lines 19-20)

"glass plates provided with an **array of** depressions or **wells** . . ." (page 16, lines 10-11)

"denatured and aliquoted into Dynatech, Immulon II™ **removeable wells**." (Example 5, page 21, lines 1-2)

"**polystyrene microfilter wells** were nitrated" (Example 6, page 22, lines 10-11)

"The **polystyrene wells** were immersed" (Example 6, page 22, lines 12-13)

"Amino-derivitized **polystyrene microfilter wells**" (Example 6, page 22, lines 28-29)

"surfaces or **wells [of glass or polystyrene surfaces]** (Example 6, page 23, line 5)

"**conventional microtiter well plates**" (Example 7, page 23, line 17)

"selected from . . . **a well**, . . . and an apparatus which comprises **a plurality of said wells**, ..." (Original claim 17)

"selected from . . . **a well**, . . ." (Original claim 21)

Thus, from the above citations, a "well" or "wells" are disclosed in the context of:

- **plastic or glass wells**
- **portion of a device for containing fluid**
- **glass plates provided with an array of wells**
- **removeable wells**
- **polystyrene microfilter wells**
- **polystyrene wells**
- **wells [of glass or polystyene surfaces]**
- **conventional microtiter well plates**
- **well and a plurality of wells (as set forth in the originally filed claims)**

Enz-7(P)(C3)

Proposed amendment with respect to "set":

Claim 3147. (First Proposal) The non-porous solid support of claim 3144 or 3145, wherein said non-porous solid support comprises a plate **or plates**, a well or wells, a microtiter well or microtiter wells, **a depression or** depressions, **a tube or** tubes, **a cuvette or** cuvettes, **a bead or** beads, or ~~a set~~ **an arrangement** of said plates, wells, depressions, tubes, cuvettes or beads.

Disclosure of "plates" in the specification to support "generic plates" include the following:

"**glass plates** provided **with** an array of **depressions or wells**" (Example 1, page 16, lines 9-10)

"**polystyrene plates** of different batches" (Example 5, page 20, lines 30-31)

". . . the analyte, was bound to **polystyrene plates** . . . (Example 5, page 21, lines 17-18)

"was applied to DDA-coated **polystyrene plates.**" (Example 6, page 22, lines 1-2)

"**conventional microtiter well plates**" (Example 7, page 23, line 17) also (Example 7, page 24, second full paragraph)

Thus, from the above citations, "generic plates" are disclosed in the context of:

- **glass plates with an array of depressions or wells**
- **polystyrene plates** (Petrie dishes)
- **conventional microtiter well plates**

"Surfaces" are disclosed three times in the specification to support the "more than one surface" limitation:

"analytes being fixed to the **surfaces** of the wells" (Example 1, page 16, line 13)

"These epoxy solutions are applied to the **surfaces** or wells," (Example 6, page 23, lines 4-5)

"These **surfaces** were found to absorb ^{3}H-labeled DNA." (Example 6, page 23, lines 8-9)

Proposed amendment with respect to "fixed or immobilized to one of said reactive sites or binding sites":

Claim 3149. (Proposed) The non-porous solid support of claim 3144 or 3145, comprising reactive sites or binding sites thereon, wherein said nucleic acid is fixed or immobilized to ~~one of~~ **said** reactive ~~sites~~ site or binding ~~sites~~ site.

With respect to the "proportional to" quantitation limitation in the claims, the specification discloses (page 4, last full paragraph) the term "proportionately" in the context of "[t]he primary recognition event and the signalling event of polynucleotide sequence based detection techniques":

> The primary recognition event and the signalling event of polynucleotide sequence based detection techniques may be coupled either directly or indirectly, **proportionately** or inversely proportionately. Thus, in such systems as nucleic acid hybridizations with sufficient quantities of radiolabeled probes, the amount of radio-activity is usually **directly proportional to the amount of analyte present.** Inversely proportional techniques include, for example, competitive immuno-assays, wherein the amount of detected signal decreases with the greater amount of analyte that is present in the signal.

At the end of the first paragraph on page 11, the specification also discloses "quantifiable report of the relative amount of analyte present":

> . . . Generation of the soluble signal provides simple and rapid visual detection of the presence of the analyte and also provides a **quantifiable report of the relative amount of analyte present**, as measured by a spectrophotometer or the like.

The citations above support the quantitation limitation directed to "proportional to."

Proposed amendment with respect to "in" or "through" a non-porous solid support:

Claim 3165. (Proposed) The non-porous solid support of claim 3145, wherein said non-porous solid support is transparent or translucent, and said non-radioactive chemical label is quantifiable in or from a fluid or solution or ~~in or through~~ **from** said non-porous solid support, said quantity being proportional to the amount or quantity of said label or labels.

With respect to the terms "iminobiotin," "hapten," and "ligand," it should be noted that in the specification beginning with the last four lines on page 7, and continuing through the first two lines on page 8, the reader is directed to David Ward's European Patent Application No. 63879:

> . . . For a review of non-radioactive signalling and bridging/signalling systems, both biotin/avidin and otherwise, see D. C. Ward et al., "Modified Nucleotides and Methods of Preparing and Using Same", European Patent application No. 63879.

A review of European Patent Application Publication No. 0 063 879 reveals that the terms "iminobiotin," "hapten," and "ligand" are disclosed in that document as follows:

For "iminobiotin"

"Although **iminobiotin** binds avidin less tightly than biotin, similar reactions can be used for its detection. Moreover, the reversibility of the **iminobiotin**-avidin interaction, by decreasing solution pH, offers significant advantages in certain applications." (EP 0063879, page 2, end of 1st ¶)

"A is biotin or **iminobiotin**;" (EP 0063879, page 6, line 5)

"Of these the preferred A moieties are biotin and **iminobiotin**." (EP 0063879, page 13, lines 26-27)

"Biotin and **iminobiotin** satisfy both of these criteria." (EP 0063879, page 13, lines 35-36)

"TABLE II Affinity Chromatography of **Iminobiotin**-dUTP and **Iminobiotinized** - DNA on Streptavidin-Sepharose" (EP 0063879, page 26)

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Exhibit 6

"Examples 5 and 6 Synthesis of **Iminobiotinyl**-UTP and **Iminobiotinyl**-dUTP" (EP 0063879, page 49)

Claim 6 "A compound in accordance with Claim 1 or 2 wherein A is **iminobiotin**." (EP 0063879, page 57)

See also Claim 37 "wherein said chemical moiety represnted by the formula . . . N is -CH=CH-CH2-NH-**iminobiotin**."
(EP 0063879, page 64)

For "hapten"

"A therefore may be any ligand which possesses these properties, including **haptens** which are only immunogenic when attached to a suitable carrier, but are capable of interacting with appropriate antibodies to produce complexes.
(EP 0063879, page 12, last four lines)

" '**haptene**-antibody sandwich technique' described by Lamm, et al., (1972)" (EP 0063879, page 38, lines 20-21)
"**haptene**-IgG interactions" (EP 0063879, page 39, line 15)

For "ligand"

"A therefore may be any **ligand** which possesses these properties, including haptens which are only immunogenic when attached to a suitable carrier, but are capable of interacting with appropriate antibodies to produce complexes.
(EP 0063879, page 12, last four lines)

Claim 4 "wherein A is a **ligand**." (EP 0063879, page 57)

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The disclaimer language was discussed at the May 20, 2004 interview with the Examiner who suggested minor changes to the proposed language. The fact of the matter is -- indirect fixation techniques, such as in situ hybridization and sandwich hybridization, and direct fixation techniques, are applicable, according to the specification, to fixing nucleic acids to a non-porous solid support. See specification, page 10, first full paragraph:

> In accordance with the practice of this invention, analytes in a biological sample are preferably denatured into single-stranded form, and then directly fixed to a suitable solid support. Alternatively, the analyte may be directly fixed to the support in double-stranded form, and then denatured. The present invention also encompasses **indirect fixation** of the analyte, **such as in situ techniques where the cell is fixed to the support** and sandwich hybridization techniques where the analyte is hybridized to a polynucleotide sequence that is fixed to the solid support. . .

Thus, the application of the disclaimer language to an array comprising various single-stranded nucleic acids fixed or immobilized to a non-porous solid support having depressions or wells is appropriate and is not new matter because nucleic acids are fixed or immobilized to a suitable solid support as disclosed in the above-quoted passage. In the course of that fixation or immobilization, in situ techniques where the cell is fixed to the support is disclaimed.

With respect to the metes and bounds of the claimed "set" comprising the non-porous solid support," the claim amendments proposed in Rejection No. 7 (Exhibit 7) should clarify the claim language, first, as to whether the set is defined by one support or the set limitation, and second, as to what is the meaning of the set if it includes one or more items other than the recited solid support.

The claim proposals in Rejection No. 7 (Exhibit 7) include:

Claim 3170. (First Proposal) ~~A set comprising the non-porous~~ **Non-porous** solid ~~support~~ **supports** of claim 3144.

Claim 3171. (First Proposal) ~~A set comprising the non-porous~~ **Non-porous** solid ~~support~~ **supports** of claim 3145.

The vaguerness/indefiniteness rejection directed to whether one, both, or neither of the limitations "directly" or "indirectly" applies to modify "immobilized" can be handled by the following proposed claim amendments:

Claim 3144. (Proposed) A non-porous solid support comprising at least one single-stranded nucleic acid directly or indirectly fixed or **directly or indirectly** immobilized thereto in hybridizable form, wherein when said nucleic acid is indirectly fixed or **indirectly** immobilized to said non-porous solid support, said indirect fixation or **indirect** immobilization is not to a cell fixed *in situ* to said non-porous solid support.

Claim 3173. (Proposed) A system comprising a non-porous solid support and at least one double-stranded nucleic acid fixed or immobilized thereto, wherein at least one nucleic acid strand of said double-stranded nucleic acid comprises at least one non-radioactive chemical label which is quantifiable or detectable, and wherein when said nucleic acid is indirectly fixed or **indirectly** immobilized to said non-porous solid support, said indirect fixation or **indirect** immobilization is not to a cell fixed *in situ* to said non-porous solid support.

For Single-Stranded / Non-Porous Solid Support:

SOLID SUPPORT -- MARKUSH -- SINGLE-STRANDED

Claim 3144. (Proposed) A non-porous solid support comprising one or more amine(s), hydroxyl(s) or epoxide(s) thereon, wherein at least one single-stranded nucleic acid is ~~directly or indirectly~~ fixed or ~~directly or indirectly~~ immobilized ~~thereto~~ in hybridizable form to said solid support via said one or more amine(s), hydroxyl(s) or epoxide(s). ~~, wherein when said nucleic acid is indirectly fixed or indirectly immobilized to said non-porous solid support, said indirect fixation or indirect immobilization is not to a cell fixed *in situ* to said non-porous solid support.~~

For Double-Stranded / Non-Porous Solid Support:

SOLID SUPPORT -- MARKUSH -- DOUBLE-STRANDED -- COVALENTLY ATTACHED LABEL

Claim 3145. (Proposed) A non-porous solid support comprising one or more amine(s), hydroxyl(s) or epoxide(s) thereon, wherein at least one double-stranded nucleic acid is ~~directly or indirectly~~ fixed or ~~directly or indirectly~~ immobilized ~~thereto,~~ to said non-porous solid support via said one or more amine(s), hydroxyl(s) or epoxide(s), and wherein ~~at least~~ one nucleic acid strand of said at least one double-stranded nucleic acid has covalently attached thereto (i) a signaling moiety, or (ii) a bridging moiety covalently or non-covalently attached to a signaling moiety. ~~comprises quantifiable or detectable non-radioactive chemical labels, wherein when said nucleic acid is indirectly fixed or indirectly immobilized to said non-porous solid support, said indirect fixation or indirect immobilization is not to a cell fixed *in situ* to said non-porous solid support.~~

For Double-Stranded / Non-Porous Solid Support:

Claim 3145X. (Proposed) A non-porous solid support comprising at least one double-stranded nucleic acid ~~directly or indirectly~~ fixed or ~~directly or indirectly~~ immobilized thereto, wherein ~~at least~~ one nucleic acid strand of said at least one double-stranded nucleic acid has covalently attached thereto (i) a signaling moiety, or (ii) a bridging moiety covalently or non-covalently attached to a signaling moiety, ~~comprises quantifiable or detectable non-radioactive chemical labels,~~ and wherein ~~when said nucleic acid is indirectly fixed or indirectly immobilized to said non-porous solid support,~~ said ~~indirect~~ fixation or ~~indirect~~ immobilization is not to a cell fixed *in situ* to said non-porous solid support.